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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/073,881	05/06/98	RAO	M T4903.CIP

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EXAMINER

KERR, J

ART UNIT	PAPER NUMBER
1633	13

DATE MAILED: 04/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/073,881	RAO ET AL.
	Examiner Janet Kerr	Art Unit 1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 07 February 2001.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-13 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.
- 11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved.
- 12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some \* c) None of:
1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

#### Attachment(s)

- 15) Notice of References Cited (PTO-892)      18) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_ .
- 16) Notice of Draftsperson's Patent Drawing Review (PTO-948)      19) Notice of Informal Patent Application (PTO-152)
- 17) Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.      20) Other: \_\_\_\_\_

***Response to Amendment***

Applicants' amendment, filed 2/7/01, has been entered.

Claim 14 has been canceled.

Claims 1-13 remain pending.

***Claim Objections***

Claim 1 is objected to because of the following informalities: on lines 15, 17, 19, and 21 the term "homogenous" should be changed to "homogeneous". Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for generating rat neural crest stem cells comprising isolating a pure, homogeneous population of rat neuroepithelial stem cells obtained from the neural tube from a rat embryo at a stage of embryonic development after closure of the neural tube comprising removing a sample of neural tube tissue from a rat at a stage of embryonic development after closure of the neural tube, dissociating cells from the sample of neural tube tissue, plating the dissociated cells in feeder-independent culture on a fibronectin substratum and in a media comprising fibroblast growth factor and chick embryo extract and inducing the isolated, pure, homogeneous population of neuroepithelial stem cells to differentiate *in vitro* into neural crest stem cells by replating the isolated, pure, homogeneous population of neuroepithelial stem cells on a fibronectin substratum and in a media comprising chick embryo extract, NGF,

FGF, EGF, and optionally BMP-2, does not reasonably provide enablement for the claim-designated method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification is enabling for a method for producing neural crest stem cells comprising the steps of obtaining a pure, homogeneous population of rat neuroepithelial stem cells obtained from the neural tube from a rat embryo at a stage of embryonic development after closure of the neural tube as recited in part (a) steps (I)-(iii) of claim 1, the method further comprising inducing the isolated, pure, homogeneous population of neuroepithelial stem cells to differentiate into neural crest stem cells in vitro by replating the neuroepithelial stem cells onto a fibronectin substrate and in a media comprising chick embryo extract, NGF, FGF, EGF, and optionally BMP-2 thereby producing neural crest stem cells as set forth in examples 17, 20, and 23 of the instant application. However, the specification is not enabling for practicing the method with any mammalian species as the specification does not provide any working examples of species other than rat, nor does the specification disclose at what developmental time point the neural tube should be isolated from other mammals. The specification clearly discloses isolating the neural tube from rat at stage E10.5 as this is the appropriate time to obtain a population of neuroepithelial stem cells which have not differentiated into particular lineages (see, e.g., page 19, Example 1, of the instant application). Moreover, the specification discloses that neural crest stem cells are a transient population of cells that arise at or around the time of neural tube closure which undergo extensive migration, and generate a prodigious array of phenotypes (see, e.g., page 46, lines 1-4 of the instant application). Thus, it is not clear at what time point the pure, homogeneous population of neuroepithelial cells can be obtained from a sample of the neural tube of other mammalian species such that neural crest stem cells are not present in the sample.

In addition, while the specification is enabling for differentiating the neuroepithelial stem cells into neural crest stem cells using the methods set forth in Examples 17, 20, and 23 of the instant application, the specification is not enabling for inducing the neuroepithelial stem cells to

differentiate into neural crest stem cells by the claimed method as the steps in the method result in the differentiation of neuroepithelial stem cells to cells beyond that of the neural crest stem cell (see, e.g., Examples 5-7 of the instant application). Moreover, the teachings of Kalyani *et al.* (*Developmental Biology*, Vol. 186, pages 202-223, 1997), in which inventor Rao is a coauthor, clearly indicates that replating neuroepithelial cells onto laminin substrates, and/or removing fibroblast growth factor and/or chick embryo extract does not result in a population on neural crest stem cells (see, e.g., pages 219-220, under the section entitled “Relationship of NEP Cells to Neural Crest Stem Cells”). Thus, in view of the state of the art at the time of filing, and in view of the experimental data set forth in the instant application, one of skill in the art could not arrive at a population of neural stem crest cells practicing the claimed method without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 is rendered vague and indefinite by the phrase “wherein said inducing comprises withdrawing a mitogen” because it is unclear if the mitogen is FGF, as recited in amended claim 1, or a different mitogen. Clarification is required.

#### *Claim Rejections - 35 USC § 102 and 103*

The declaration submitted under 37 CFR 1.132 filed 2/7/01 is sufficient to overcome the rejection of claims 1-3, 5, 6, and 8 under 35 U.S.C. 102 (a) and based upon Rao *et al.*, and the

rejection of claims 4, 7, and 9-13 under 35 U.S.C. 103(a) based upon Rao *et al.* taken with Varley *et al.*.

In addition, In view of the amendments to the claims, the rejection of claims 1, 2, and 14 under 35 U.S.C. 102(b) based upon Ray *et al.*, the rejection of claims 1, 6-8, and 14 under 35 U.S.C. 102(e) based upon Anderson *et al.* (both patents), and the rejection of claims 9-13 under 35 U.S.C. 103(a) based upon Ray *et al.* taken with Varley *et al.*, have been withdrawn.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to

Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

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